

# Lamivudine/Zidovudine



**Brand Name:** Combivir

**Drug Class:** Nucleoside Reverse Transcriptase Inhibitors

## Drug Description

Lamivudine/zidovudine is a fixed-dose tablet containing two synthetic nucleoside analogues: lamivudine and zidovudine. Each tablet contains 150 mg of lamivudine and 300 mg of zidovudine, each of which inhibits HIV-1 viral reverse transcriptase. [1]

## HIV/AIDS-Related Uses

Lamivudine/zidovudine was approved by the FDA on September 27, 1997, for use in combination with other antiretroviral agents for the treatment of HIV infection. Lamivudine/zidovudine tablets are an alternate regimen to lamivudine and zidovudine given as separate formulations.[2] [3]

Lamivudine is used with zidovudine for postexposure prophylaxis of HIV infection in healthcare workers and other individuals exposed occupationally via percutaneous injury or mucous membrane or nonintact skin contact with blood, tissues, or other body fluids associated with a risk for HIV transmission.[4]

## Pharmacology

Lamivudine and zidovudine each inhibit viral reverse transcriptase (RT), an enzyme HIV requires in order to replicate, by incorporating into viral DNA and terminating the viral DNA chain. (For more information, see the individual drug records for lamivudine and zidovudine.)

Lamivudine is a synthetic nucleoside analogue that is phosphorylated intracellularly to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). In vitro, lamivudine with zidovudine had synergistic antiretroviral activity.[5] L-TP, also referred to as 3TC-TP, is a structural analogue of deoxycytidine triphosphate (dC-TP), the natural substrate for viral RT. L-TP competes with naturally occurring dC-TP for incorporation into viral DNA by reverse transcriptase and once incorporated, causes premature termination of viral DNA synthesis.[6]

Following oral dosing, lamivudine is rapidly

absorbed. Absolute bioavailability in adults was 86% for the tablet dosage form. Lamivudine is extensively distributed. It crosses the blood-brain barrier and is distributed in the cerebrospinal fluid (CSF). The ratio of CSF/plasma concentration of lamivudine as reported by the manufacturer is 0.12 (range 0.04 to 0.47). Plasma protein binding is less than 36%. Lamivudine serum half-life is 2.5 +/- 0.5 hours.[7] About 70% of an intravenous dose is excreted unchanged in the urine. Metabolism is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose in six adults, 5.2% of the metabolite was excreted in the urine. In most single-dose studies in infected patients, the mean elimination half-life ranged from 5 to 7 hours.[8]

Zidovudine is also a synthetic nucleoside analogue that is phosphorylated intracellularly to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP).[9] ZDV-TP appears to compete with thymidine triphosphate for the RT enzyme and incorporation into viral DNA. After incorporation of ZDV-TP, DNA synthesis is prematurely terminated because the 3'-azido group in the zidovudine molecule prevents further 5' to 3' phosphodiester linkages. In vitro, zidovudine demonstrates synergistic activity with abacavir,[10] delavirdine, didanosine, indinavir, nelfinavir, nevirapine, ritonavir, saquinavir, and zalcitabine, and additive activity with interferon-alpha.[11]

Zidovudine is rapidly absorbed from the gastrointestinal tract and extensively distributed, with peak serum concentrations occurring within 0.4 to 1.5 hours; however, absorption following oral administration shows considerable individual variability. In fasting adults, about 64% of an oral dose reaches systemic circulation as unchanged drug. There is limited information on the distribution of zidovudine in the body, but the drug appears to be widely distributed. Zidovudine is distributed into the CSF.[12] The ratio of CSF/plasma concentration of zidovudine as reported by the manufacturer is 0.6 (range 0.04 to 2.62).[13] However, animal studies indicate that, although zidovudine distributes easily into the CSF, distribution into the brain interstitial fluid may be

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## Pharmacology (cont.)

minimal.[14] Plasma protein binding is low and elimination is primarily by hepatic metabolism. The major metabolite is 3'-azido-3'-deoxy-5'-O-beta-D-glucopyranuronosylthymidine (GZDV). Some 14% to 18% of unchanged zidovudine and 72% to 74% of the drug as its major metabolite, GZDV, are eliminated through the urine.[15]

One lamivudine/zidovudine tablet is bioequivalent to one lamivudine tablet (150 mg) plus one zidovudine tablet (300 mg) following single-dose administration to healthy adults.[16]

Lamivudine/zidovudine is in FDA Pregnancy Category C. No adequate or well-controlled studies of the combination drug have been done in pregnant women. A study of zidovudine therapy in women in the last trimester of pregnancy showed that although this drug does cross the placenta, there was no evidence of drug accumulation, and zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Studies in laboratory rabbits and rats have shown that lamivudine crosses the placenta, with evidence of embryo lethality in rabbits but not in rats at dosage levels many times higher than the corresponding dose for humans. Lamivudine/zidovudine should be used in pregnancy only if the potential benefits outweigh the risks. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to lamivudine/zidovudine and other antiretrovirals. Physicians may register patients by calling (800) 258-4263. Zidovudine is excreted in human milk, and lamivudine is excreted in the milk of laboratory animals.[17]

Lamivudine-resistant isolates of HIV-1 have been selected in vitro and have also been isolated from patients treated with lamivudine or lamivudine plus zidovudine. The resistant isolates showed reduced susceptibility to lamivudine. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment

with zidovudine and lamivudine.

Lamivudine/zidovudine combination therapy delayed the emergence of mutations conferring zidovudine resistance. HIV strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy.[18]

Cross-resistance to didanosine and zalcitabine has been seen in patients treated with lamivudine alone or in combination with zidovudine. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple RT inhibitors, including lamivudine, have emerged. Multiple drug resistance, including resistance to lamivudine, didanosine, stavudine, zalcitabine, and zidovudine, has been observed in HIV isolates from some patients treated for more than 1 year with zidovudine plus didanosine or zalcitabine. The pattern of mutations with combination therapy was different from that seen with zidovudine monotherapy.[19]

Cross-resistance between zidovudine and HIV protease inhibitors is unlikely because the drugs have different target enzymes. The potential of cross-resistance between zidovudine and nonnucleoside reverse transcriptase inhibitors (NNRTIs) is also considered to be low since the drugs bind at different sites on the reverse transcriptase and have different mechanisms of action.[20]

## Adverse Events/Toxicity

Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues alone or in combination. These conditions are sometimes fatal. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Caution should be exercised in any patient with known risk factors for liver disease; however, cases have been reported in patients with no known risk factors. Treatment with lamivudine/zidovudine should be suspended in any patient who develops clinical or laboratory findings that suggest the presence of lactic acidosis or pronounced hepatotoxicity.[21] Granulocytopenia and anemia are the most frequent adverse effects associated with zidovudine therapy. Zidovudine has been associated with hematologic toxicity,

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## Adverse Events/Toxicity (cont.)

including neutropenia and severe anemia, particularly in patients with advanced HIV disease. Myopathy and myositis have occurred with prolonged use of zidovudine and may occur during therapy with lamivudine/zidovudine.

Post-treatment exacerbations of hepatitis B virus (HBV) infections have been reported in both HIV and non-HIV infected patients treated with lamivudine for chronic HBV when lamivudine therapy was discontinued.[22] Deterioration of liver disease has been reported in some patients coinfecting with HIV and HIV when lamivudine therapy was discontinued.[23]

Immune reconstitution syndrome has been reported in patients receiving anti-HIV therapy, including lamivudine/zidovudine. Patients who exhibit an inflammatory response to indolent or residual opportunistic infections may require further evaluation before initiating certain anti-HIV regimens.[24]

Other reported adverse events occurring in clinical trials of lamivudine/zidovudine affected the following body systems: body as a whole (headache, malaise, fatigue, fever, chills); digestive (nausea, diarrhea, vomiting, anorexia and/or decreased appetite, abdominal pain and cramps, dyspepsia); nervous system (neuropathy, insomnia and other sleep disorders, dizziness, depressive disorders); respiratory (nasal signs and symptoms, cough); skin (rash); and musculoskeletal (musculoskeletal pain, myalgia, arthralgia). Adverse events reported during post-approval use of lamivudine/zidovudine or either of the component drugs occurred in the following body systems: body as a whole (redistribution or accumulation of body fat); cardiovascular (cardiomyopathy); endocrine and metabolic (gynecomastia, hyperglycemia); gastrointestinal (oral mucosal pigmentation, stomatitis); general (vasculitis, weakness); hemic and lymphatic (aplastic anemia, anemia, lymphadenopathy, pure red cell aplasia, splenomegaly); hepatic and pancreatic (lactic acidosis and hepatic steatosis, pancreatitis); hypersensitivity (sensitization reactions, including anaphylaxis, urticaria); musculoskeletal (muscle weakness, CPK elevation,

rhabdomyolysis); nervous (paresthesia, peripheral neuropathy, seizures); respiratory (abnormal breath sounds, wheezing ); and skin (alopecia, erythema multiform, Stevens-Johnson syndrome).[25]

## Drug and Food Interactions

Lamivudine/zidovudine tablets may be administered with or without food. Administering the drug with food did not alter the area under the concentration-time curve (AUC) for lamivudine or zidovudine, as compared to administration under fasting conditions.[26]

Because lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another, lamivudine/zidovudine should not be coadministered with zalcitabine.[27] Lamivudine exposure (AUC) was increased by 44% and lamivudine renal clearance was decreased by 30% when co-administered with sulfamethoxazole/trimethoprim. Concurrent administration of lamivudine and zidovudine in one small study resulted in a 39% increase in peak plasma concentration of zidovudine with no change observed in AUC. Concurrent administration of lamivudine with indinavir and zidovudine resulted in a 6% decrease in AUC of lamivudine, no change in AUC of indinavir, and a 36% increase in AUC of zidovudine. No adjustment in dose is necessary. Concurrent administration of lamivudine with drugs associated with pancreatitis (alcohol, didanosine, IV pentamidine, sulfonamides, and zalcitabine) or with drugs associated with peripheral neuropathy (dapsone, didanosine, isoniazid, stavudine, and zalcitabine) should be avoided or used cautiously.[28]

Zidovudine may interact with atovaquone, clarithromycin, fluconazole, methadone, phenytoin, probenecid, rifampin, and valproic acid. The hematologic toxicity of zidovudine may be increased when zidovudine is coadministered with bone marrow depressant agents such as ganciclovir or interferon-alpha and others, or with blood dyscrasia-causing medications, cytotoxic agents, or radiation therapy. Medications that are metabolized by hepatic glucuronidation such as acetaminophen, aspirin, benzodiazepines, cimetidine, indomethacin, morphine, and sulfonamides may in theory increase the risk of toxicity of zidovudine or the other



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## Drug and Food Interactions (cont.)

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medication.[29] An antagonistic relationship between zidovudine and stavudine, doxorubicin, and ribavirin has been reported in vitro. Concomitant use of zidovudine with any of these three drugs should be avoided.[30] Coadministration of zidovudine and stavudine is not recommended due to limited evidence of in vivo antagonism.[31]

In vitro studies show that ribavirin reduces the phosphorylation of pyrimidine nucleoside analogues, including lamivudine and zidovudine. No evidence of an interaction was seen when ribavirin was coadministered with lamivudine/zidovudine in patients coinfecting with HIV and hepatitis C virus (HCV). However, hepatic decompensation (some fatal) has occurred in patients coinfecting with HIV and HCV receiving combination anti-HIV therapy with interferon alfa and ribavirin.[32]

Combivir is a fixed dose formulation of lamivudine and zidovudine and ordinarily should not be administered concomitantly with lamivudine, zidovudine, or Trizivir, a fixed-dose combination of abacavir sulfate, lamivudine, and zidovudine.[33]

## Contraindications

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Lamivudine/zidovudine tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.[34]

Due to the fixed-dose formulation of lamivudine/zidovudine, there is no way to accommodate the dosage reduction of zidovudine that may be necessary in individuals with impaired liver function or the dosage adjustment of both lamivudine and zidovudine that may be necessary in those with renal insufficiency (creatinine clearance less than 50 ml/min). Additionally, dosage adjustments cannot be made for patients younger than 12 years old or for any patient with special dosing requirements. Lamivudine/zidovudine is not recommended for these patients.[35]

## Clinical Trials

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For information on clinical trials that involve Lamivudine/Zidovudine, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Lamivudine/Zidovudine AND HIV Infections.

## Dosing Information

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Mode of Delivery: Oral.[36]

Dosage Form: Film-coated tablets containing lamivudine 150 mg and zidovudine 300 mg.[37]

The recommended dose of lamivudine/zidovudine for adults and adolescents at least 12 years of age is one tablet twice daily. Lamivudine/zidovudine should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance less than 50 ml/min), those experiencing dose-limiting adverse events, or those with impaired hepatic function or liver cirrhosis.[38]

Storage: Lamivudine/zidovudine tablets should be stored between 2 C and 30 C (36 F and 86 F).[39]

## Chemistry

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CAS Name: Lamivudine: 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-, (2R-cis)-[40]

Zidovudine: Thymidine, 3'-azido-3'-deoxy-[41]

CAS Number: Lamivudine: 134678-17-4[42]

Zidovudine: 30516-87-1[43]

Molecular formula: Lamivudine: C<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S; Zidovudine: C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>[44]

Lamivudine: C41.91%, H4.84%, N18.33%, O20.94%, S13.99%; Zidovudine: C44.94%, H4.90%, N26.21%, O23.95%[45]

Molecular weight: Lamivudine: 229.26; Zidovudine: 267.24[46]

# Lamivudine/Zidovudine



## Chemistry (cont.)

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Melting point: Lamivudine: 160-162 C;  
Zidovudine: 106-112 C[47]

Physical Description: Film-coated tablets containing 150 mg of lamivudine and 300 mg of zidovudine plus inactive ingredients.[48]

Solubility: Lamivudine: 70 mg/ml in water at 20 C;  
Zidovudine: 20.1 mg/ml in water at 25 C.[49]

## Further Reading

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## Manufacturer Information

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Lamivudine/Zidovudine  
GlaxoSmithKline  
5 Moore Drive  
Research Triangle Park, NC 27709  
(888) 825-5249

Combivir  
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## For More Information

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Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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